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Continuous multiorgan variability analysis to track severity of organ failure in critically ill patients☆

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Abstract

Purpose: The purpose of this study is to evaluate the utility of using continuous heart rate variability (HRV) and respiratory rate variability (RRV) monitoring for (*a*) tracking daily organ dysfunction in critically ill patients and (*b*) identifying patterns of variability changes during onset of shock and resolution of respiratory failure.

Materials and Methods: Thirty-three critically ill patients experiencing respiratory and/or cardiac failure underwent continuous recording of their electrocardiogram and capnogram (CO_2) waveforms from admission or intubation until discharge (maximum 14 days). HRV and RRV were computed in 5-minute overlapping windows, using Continuous Individualized Multi-organ Variability Analysis software. Multiple organ dysfunction scores were recorded daily. HRV and RRV trajectories were characterized during onset of shock and resolution of respiratory failure.

Results: Both HRV and RRV decreased with increasing severity of multiple organ dysfunction scores for a variety of variability metrics. A decline in several measures of HRV and no decline in RRV were observed before onset of shock (n = 6). In contrast, during resolution of respiratory failure, an increase in RRV was observed in patients who successfully passed extubation (n = 12), with no change in RRV in those who subsequently failed extubation (n = 2).

Conclusions: There is an association between reduced HRV and RRV and increasing organ dysfunction in critically ill patients. The significance of observing trends of decreasing HRV (with onset of shock) and increasing RRV (with resolution of respiratory failure) merits further investigation.

☆ Competing interests: Andrew J.E. Seely is founder and Chief Science Officer of Therapeutic Monitoring Systems, Inc, created to commercialize patented Continuous Individualized Multi-organ Variability Analysis technology, with the objective of delivering variability-directed clinical decision support to improve quality and efficiency of care. Geoffrey C. Green is currently employed by Therapeutic Monitoring Systems, Inc, in the position of Product Manager.

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1. Introduction

Prognostication of severity of illness has long been a subject of investigation by intensivists and scientists. Several sophisticated scoring systems exist, which "quantify the generic severity of illness early during the course of the intensive care unit (ICU) stay and express that severity as a probability of survival for a given patient" [1]. Such tools (e.g, references [2-4]) are very important for the initial evaluation and planning of a course of care. However, their usefulness is reduced when trying to foretell what will happen to an individual patient in the ICU, for example, if they will develop new organ dysfunction or if they are responding to a given therapy [1]. Organ dysfunction scores such as the multiple organ dysfunction syndrome (MODS) score [5] and sequential organ failure assessment (SOFA) score [6] are objective measures of a patient's severity of illness and offer simplification to the complexity of their current physiologic state. Those measures, if monitored daily and compared against a baseline value at the time of admission or aggregated over the course of ICU stay, can offer additional insight into clinical deterioration or improvement [1,7,8].

Complex systems science has been hypothesized to provide a complementary approach for the description and management of organ dysfunction in the critically ill patient [9]. Clinically valuable information, hidden within the rhythms of the body, can be uncovered by advanced techniques rooted in mathematical physics and nonlinear dynamics. For example, electrocardiogram (ECG) and capnogram waveforms may be used to measure heart rate variability (HRV) and respiratory rate variability (RRV), derived from the time series of interbeat and interbreath intervals. Numerous studies reviewed previously [10] demonstrate how these time series are characterized by specific patterns that can be used to discriminate between healthy and pathologic patients and demonstrate that degree of variability correlates with illness severity.

Focusing on critically ill patients, the clinical significance of reduced HRV was demonstrated in association with sepsis and septic shock [11-13] and the evaluation of its severity [14,15]. Moreover, HRV analysis has shown prognostic capabilities in adult septic patients as an early marker of MODS [16] and an early predictor of death in emergency departments [17]. Considering pediatric applications, altered HRV was present in children developing sepsis or septic shock [18] and correlated with illness severity and organ dysfunction in pediatric ICU patients [19,20]. Similarly, the clinical significance of altered respiratory variability has been demonstrated in the detection of respiratory dysfunction associated with asthma [21-23], sleep apnea [24], and panic disorder [25-27]. In the ICU, recent investigations have focused on respiratory variability as a novel predictor of successful weaning of patients from mechanical ventilation [28-33].

The value of tracking variability over time was demonstrated in noncritically ill patients by Voss [34], who conducted HRV studies in pregnant women and athletes spanning weeks and months. In the ICU setting, however, the potential for improving individualized patient care through variability monitoring remains largely unexplored. This is primarily due to challenges associated with the continuous acquisition, transfer, and analysis of physiologic waveforms from patient monitoring systems [35]. For this reason, most prior studies have assessed HRV for short intermittent epochs of 5 to 15 minutes. Among the few focusing on longitudinal analysis of variability in the ICU, Papaioannou et al [36] evaluated daily variability over the course of a patient's ICU stay, correlating HRV with mortality and organ dysfunction (as estimated by daily SOFA score), and Kasaoka et al [37] pursued real-time HRV monitoring in the ICU, performing analyses of variability over 2 different conditions (mechanical vs spontaneous breathing and response to shock). Recently, in this journal, we presented a study describing a methodology and reported on the feasibility of continuous simultaneous HRV and RRV monitoring in critically ill patients [38] using Continuous Individualized Multiorgan Variability Analysis (CIMVA), a software tool developed by our group for continuous variability monitoring [39].

In the present study, we sought to combine continuous multiorgan waveform acquisition with longitudinal variability analysis and relate this novel information stream with patient status (e.g, MODS score) and outcomes (e.g., onset of shock and resolution of respiratory failure). We hypothesized that continuous variability monitoring in the ICU can provide improved ability to predict clinical improvement or deterioration (ie, detect clinical trajectory), potentially leading to real time prognostication in this critical care setting. The overall aims of this study were to explore the feasibility of using CIMVA in an ICU setting to (1) evaluate the association between daily MODS scores and daily measures of HRV and RRV and (2) evaluate the pattern of variability changes as a predictor of the onset of shock (i.e, initiation of vasopressors) and resolution of respiratory failure (ie, extubation).

2. Materials and methods

2.1. Patients

2.1.1. Enrollment

The study was performed in the 32-bed ICU of a single tertiary care hospital (Ottawa General Hospital). The patient population in the unit can be characterized as combined medical/surgical (no trauma). Critically ill patients experiencing respiratory and/or cardiac failure were selected to have their ECG and capnogram (CO_2) waveforms continuously recorded while in the ICU. Thirty-three patients were enrolled between June 2009 and November 2009.

2.1.2. Consent

This study was approved by the Ottawa Hospital Research Ethics Board. Waived consent was obtained as the study was observational, data were de-identified, and we wished to eliminate the potential for bias and limitations to external validity.

2.1.3. Inclusion criteria

Patients admitted to ICU within 48 hours with respiratory and/or cardiac failure and expected period on study greater than 72 hours were included. *Respiratory failure* was defined as the need for mechanical ventilation and a Pa_{O_2}/fraction of inspired oxygen less than 300. *Cardiac failure* was defined as hypotension requiring 2 or more consecutive hours of vasopressors (norepinephrine or epinepherine >5 μg/kg per minute, phenylephrine >50 μg/min, or vasopressin >0.03 U/min).

2.1.4. Exclusion criteria

Patients with chronic atrial fibrillation (determined from past medical history reported by the patient/family to the treating team) and/or transferred from another ICU were excluded.

2.2. Clinical data collection

The following parameters were recorded for each patient once (upon enrollment into the study): demographic information, ICU admission diagnosis, comorbidities, and Acute Physiology and Chronic Health Evaluation II score on the day of admission. Other parameters recorded throughout the study included date and time of extubation, total length of stay (if within 30 days), survival status in ICU and at 30 days after ICU admission, need for reintubation, and need for tracheostomy.

The following parameters were recorded daily for each patient: MODS scores, ventilator settings, presence and dosages of inotropes, and/or vasopressors.

2.3. Waveform data collection

Continuous ECG and capnogram waveforms (125 Hz) were captured from Philips IntelliVue MP70 monitors as described previously [38]. Electrocardiographic monitoring was initiated within 36 hours of ICU admission and continued until ICU discharge or a maximum of 14 days; CO_2 monitoring was initiated when Philips IntelliVue CO_2 measurement modules were applied at time of enrollment and continued until extubation or a maximum of 14 days.

2.4. Continuous Individualized Multi-organ Variability Measurement processing

Continuous Individualized Multi-organ Variability Measurement software was used to generate continuous HRV and RRV time series for each patient, a process that has been described in detail previously [38]. Briefly, the following data processing stages are performed over continuous windows of time: (1) automatic beat detection[1] and breath detection, (2) creation of R-R interval (RRI) time series and interbreath interval time series, (3) identification of atrial fibrillation (ECG only), (4) identification and elimination of artifact and outliers, (5) variability analysis, and (6) post-processing to remove poor quality windows. The CIMVA analysis was performed with a sliding window length of 5 minutes (50% overlap between adjacent windows) throughout the duration of the input RRI and interbreath interval time series data. This resulted in continuous HRV and RRV outputs at a sampling interval of 2.5 minutes. A wide panel of variability measures was calculated, including those from time domain, frequency domain, time-frequency domain, entropy domain, and scale-invariant domain [38]. Frequency domain measures are not reported for RRV.

2.5. Analysis of CIMVA variability output

Any patient who experienced intermittent episodes of atrial fibrillation or other arrhythmias (eg, trigeminy, bigeminy) during the study period were excluded from all HRV analyses but included in RRV analyses.

2.5.1. Analysis of variability in association with organ dysfunction

Variability metrics (calculated as the average of all 5-minute CIMVA analysis windows in a day, from midnight to midnight) were computed for each day of each patient's ICU stay. In order for a patient-day to be included in the analysis, the following criteria had to be met: (*a*) at least 80% of the 5-minute CIMVA analysis windows had to survive the postprocessing quality filter and (*b*) the MODS score for a given patient-day had to be composed of at least 2 of the 6 constituent organ system scores (cardiovascular, respiratory, hematologic, liver, renal, and neurological). All patient-days meeting these criteria were then categorized by severity of organ dysfunction recorded on that day as follows: low MODS (0-2 inclusively), medium MODS (3-7 inclusively), or high MODS (>7). Within the patient-days in each category, the variability values were averaged.

2.5.2. Statistical analysis

For each variability measure, the Kruskal-Wallis test (nonparametric analysis of variance [ANOVA]) was used to compare the medians among low, medium, and high MODS. For those measures rejecting the null hypothesis of equal median among the 3 groups, a post hoc analysis was performed using the Wilcoxon 2-sided rank sum test, to test the equality between the medians of each pair of groups. In particular, for each variability measure, the statistical test was

[1] The data acquisition system provided an ECG waveform of 125 Hz, which is less than the native resolution (1000 Hz) of the patient monitor. However, this system also provided beat annotations harvested simultaneously that were calculated using the higher resolution (ie, the RRI time series had a time resolution of 0.001 s, not 0.008 s).

run 3 times, comparing (i) low MODS vs medium MODS, (ii) medium MODS vs high MODS, and (iii) low MODS vs high MODS. The *P* values reported for each test represent the probability of observing the given result by chance if the null hypothesis is true. An α value of .05 was used to determine statistical significance. When reporting the results of multiple statistical tests (one for each variability measure —24 for HRV and 20 for RRV), one must pay particular attention to multiple comparison testing and the possibility of false positives (ie, those measures that report a meaningful association when in fact none exists). To address this, we used the false discovery rate (FDR) method of Benjamini and Yekutieli [40] with a rate of 0.05.

2.5.3. Trajectory of variability before onset of shock and extubation

We wished to investigate the time trajectory of variability in patients who experienced onset or resolution of organ failure. We elected to focus on (*a*) shock episodes, defined by initiation of vasopressors (an example of organ failure onset), and (*b*) extubation (an example of organ failure resolution). Individual patient HRV and RRV trajectories were summarized averaging the 5-minute variability windows over nonoverlapping 2-hour periods leading up to and continuing after the event of interest (for a total of 18 hours before the event of interest). The mean across all included patients at each point (Δt = 2 hours) was then computed. In the case of shock, HRV data were reported for an additional 6 hours after shock onset.

3. Results

3.1. Demographic data

In total, 33 patients were enrolled in the study. Demographic information for these patients is provided in Bradley et al [38]. At the onset of monitoring, the most common pattern of organ failure was simultaneous respiratory and cardiac failure (n = 23), compared with just respiratory (n = 7) or just cardiac (n = 3) failure. Mean number of days enrolled in the study was 11.0 (±3.6). Seven patients died within the 14-day monitoring period, and another 3 died within 30 days (30-day mortality rate of 30.3%).

3.2. Analysis of variability in association with organ dysfunction

In total, 189 days of patient ICU data was included in the HRV analysis, with low, medium, and high MODS

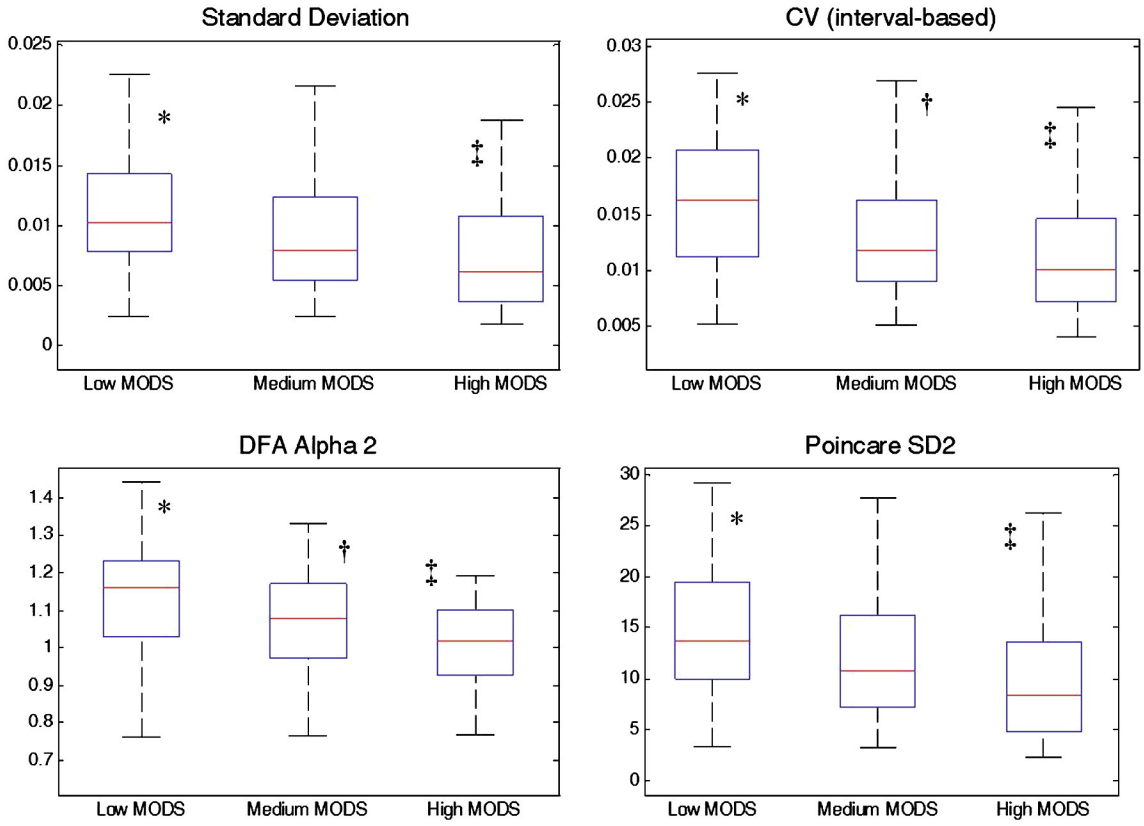

Fig. 1 Box plot of daily HRV and MODS severity. Low (MODS 0-2; n = 51 days), medium (MODS 3-7; n = 106 days), and high (MODS >7; n = 32 days). In each plot, the central mark is the median, the box edges are the 25th and 75th percentiles, and the box whiskers extend to the most extreme data points not considered as outliers.

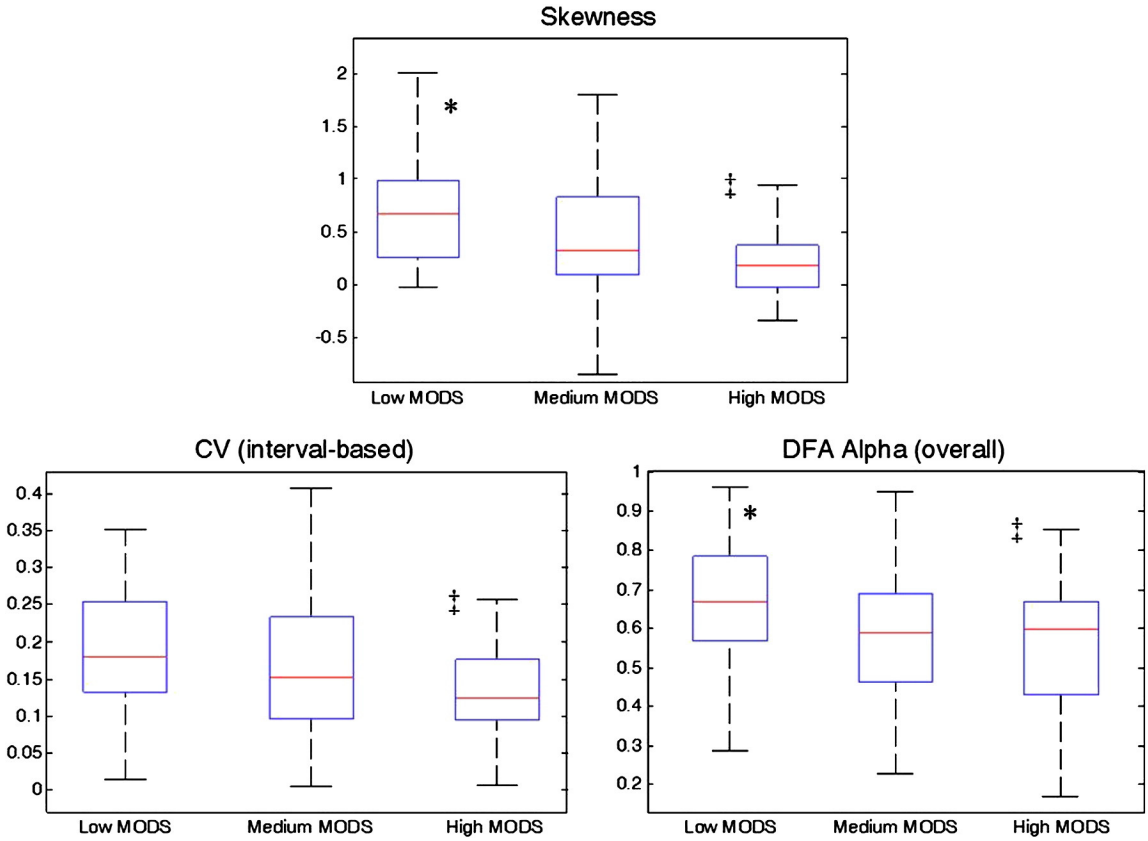

Fig. 2 Box plot of daily RRV and MODS severity. Low (MODS 0-2; n = 38 days), medium (MODS 3-7; n = 92 days), and high (MODS > 7; n = 44 days). In each plot, the central mark is the median, the box edges are the 25th and 75th percentiles, and the box whiskers extend to the most extreme data points not considered as outliers.

categories consisting of 51, 106, and 32 patient days, respectively. One hundred seventy-four days were included in the RRV analysis, with low, medium, and high MODS categories consisting of 38, 92, and 44 days, respectively. Mean daily HRV and RRV were generally higher on days with low MODS scores (least sick patients) compared with days with medium or high MODS scores (sickest patients), as shown in Figs. 1 and 2 for selected measures of HRV and RRV, respectively. The summaries of HRV and RRV measures are shown in Table 1 and Table 2, along with the results of the nonparametric ANOVA tests (and where applicable, Wilcoxon rank sum tests).

3.2.1. Heart rate variability and organ failure

For several measures of HRV (10/24; see Table 1), significant differences were observed in mean daily variability between the MODS categories. Considering this subset of measures, 8 of 10 tests rejected the null hypothesis of equal medians in distinguishing low vs medium MODS, 4 of 10 tests rejected the null hypothesis of equal medians in distinguishing medium vs high MODS, and 10 of 10 tests rejected the null hypothesis of equal medians in distinguishing low vs high MODS. For the original nonparametric ANOVA test, when adjusted for FDR of 5%, 5 of 24 variability measures remained significant (using an adjusted P = .0024)—coefficient of variation, power law y-intercept (frequency-based), detrended fluctuation analysis (DFA) α (overall), DFA α_2, and Poincare SD2.

3.2.2. Respiratory rate variability and organ failure

A few significant differences between the MODS categories were observed in mean daily RRV (5/20; see Table 2). Considering this subset of measures, 4 of 5 tests rejected the null hypothesis of equal medians in distinguishing low vs medium MODS, 0 of 5 tests rejected the null hypothesis of equal medians in distinguishing medium vs high MODS, and 5 of 5 tests rejected the null hypothesis of equal medians in distinguishing low vs high MODS. For the original nonparametric ANOVA test, when adjusted for FDR of 5%, 1 of 20 variability measures (skewness) remained significant (using an adjusted P = .000575).

3.3. Trajectory of variability before onset of shock and extubation

3.3.1. Onset of shock

Six patients who experienced shock had valid data for HRV analysis (ie, 18 hours of heart rate monitoring before onset of shock). As shown in Fig. 3, there was a declining trajectory of HRV before the onset of shock and an observed

Table 1 Daily HRV results for patient-days with low, medium, and high MODS

HRV (units)	L MODS (0-2)		M MODS (3-7)		H MODS (>7)		*P* value for ANOVA test	Wilcoxon rank sum *P* values		
	n = 51		n = 106		n = 32			L-M	M-H	L-H
	Median	IQR	Median	IQR	Median	IQR				
Mean (s)	0.66	0.599-0.72	0.624	0.568-0.727	0.637	0.579-0.694	.457	NA	NA	NA
SD (s)	0.0102	0.00788-0.0143	0.00797	0.00552-0.0124	0.00614	0.0037-0.0108	.004	.00774 *	.106	.00715 ‡
RMSSD (s)	0.00539	0.00382-0.00692	0.00472	0.00325-0.0069	0.00441	0.0032-0.0068	.415	NA	NA	NA
Skewness (none)	0.0344	−0.132-0.238	−0.0129	−0.218-0.156	−0.0907	−0.255-0.001	.054	NA	NA	NA
Kurtosis (none)	3.82	3.41-4.93	4.15	3.53-5.9	5.2	3.91-7.75	.015	.163	.0444 †	.00346 ‡
CV (none)	0.0163	0.0112-0.0208	0.0118	0.009-0.0163	0.01	0.0072-0.0145	<.001 [a]	.00379 *	.0266 †	.000333 ‡
Power law slope—frequency based	−0.104	−0.145 to −0.064	−0.0964	−0.145 to −0.0576	−0.0992	−0.136 to −0.0394	.765	NA	NA	NA
Power law y-intercept—frequency based (s^2/log Hz)	3.1	2.75-3.32	2.76	2.34-3.15	2.61	1.98-3.03	.001 [a]	.00278 *	.132	.000852 ‡
Power law x-intercept—frequency based (log Hz)	12.1	−9.46-26.2	4.91	−5-19.3	4.94	−3.78-17.8	.402	NA	NA	NA
Power law slope—histogram based	−0.634	−0.661 to −0.596	−0.653	−0.718 to −0.609	−0.696	−0.748 to −0.607	.022	.0344 *	.21	.012 ‡
Power law y-intercept—histogram based (none)	−4.38	−4.58 to −4.15	−4.57	−4.99 to −4.24	−4.74	−5.18 to −4.33	.004	.0104 *	.14	.00225 ‡
Power law x-intercept—histogram based (log s)	−7.25	−7.42 to −6.91	−7.15	−7.39 to −6.92	−7.13	−7.34 to −6.86	.722	NA	NA	NA
DFA AUC (none)	−2.82	−3.08 to −2.63	−3.03	−3.31 to −2.72	−3.13	−3.54 to −2.72	.025	.0165 *	.317	.0374 ‡
DFA α overall (none)	1.16	1.05-1.24	1.1	1.02-1.19	1.05	0.929-1.12	.002 [a]	.066	.0139 †	.000974 ‡
DFA α 1 (none)	1.04	0.799-1.26	0.981	0.784-1.18	0.957	0.7-1.11	.384	NA	NA	NA
DFA α 2 (none)	1.16	1.03-1.23	1.08	0.971-1.17	1.02	0.926-1.1	<.001 [a]	.0282 *	.00649 †	.000127 ‡
Approximate entropy (none)	0.981	0.931-1.03	0.997	0.934-1.06	1.02	0.955-1.12	.120	NA	NA	NA
Sample entropy (none)	1.46	1.31-1.71	1.57	1.44-1.8	1.58	1.35-1.8	.088	NA	NA	NA
LF/HF ratio (none)	2.29	1.17-4.16	2.29	1.15-3.86	1.73	0.957-3.91	.546	NA	NA	NA
LF power (n.u.)	18.3	5.91-31.2	9.23	4.28-25.5	8.58	2.93-28.1	.246	NA	NA	NA
HF power (n.u.)	7.97	4.31-18.4	5.98	3.12-12.5	5.67	2.96-13	.263	NA	NA	NA
Wavelet AUC (none)	−35.5	−37.8 to −32.7	−37.2	−41.5 to −33.3	−37.6	−43.1 to −32.8	.077	NA	NA	NA
Poincare SD1 (none)	3.82	2.71-4.9	3.34	2.3-4.88	3.12	2.27-4.8	.419	NA	NA	NA
Poincare SD2 (none)	13.7	9.93-19.5	10.8	7.15-16.2	8.34	4.74-13.6	.002 [a]	.00662 *	.0868	.00247 ‡

Median and interquartile range are shown. For each measure, results of nonparametric ANOVA test are shown. Where the null hypothesis of equal median among the L, M, and H groups are rejected ($P < .05$), a post hoc Wilcoxon rank sum test was run to test for equality between groups pairs (low-medium, medium-high, and low-high). n indicates the number of days; L, low; M, medium; H, high; IQR, interquartile range; NA, not applicable; AUC, area under curve.

[a] Measures that remained significant after adjustment for the FDR are indicated.

* $P < .05$ was deemed to be statistically significant between low and medium.

† $P < .05$ was deemed to be statistically significant between medium and high.

‡ $P < .05$ was deemed to be statistically significant between low and high.

Table 2 Daily RRV results for patient days with low, medium, and high MODS

RRV (units)	L MODS (0-2)		M MODS (3-7)		H MODS (>7)		*P* value for ANOVA test	Wilcoxon rank sum *P* values		
	n = 38		n = 92		n = 44			L-M	M-H	L-H
	Median	IQR	Median	IQR	Median	IQR				
Mean (s)	3.5	2.95-3.99	3.35	2.82-4.03	3.41	2.94-4.37	.735	NA	NA	NA
SD (s)	0.589	0.431-0.938	0.494	0.275-0.863	0.485	0.33-0.684	.149	NA	NA	NA
RMSSD (s)	0.746	0.488-1.21	0.643	0.347-1.13	0.592	0.431-0.917	.293	NA	NA	NA
Skewness (none)	0.664	0.255-0.996	0.319	0.0885-0.826	0.195	−0.0284-0.38	.001 [a]	.0147 *	.0533	.0000676 ‡
Kurtosis (none)	4.3	3.69-5.08	4.59	3.41-5.7	3.74	3.33-5.36	.184	NA	NA	NA
CV (none)	0.18	0.132-0.254	0.152	0.0956-0.234	0.125	0.0948-0.177	.035	.0805	.292	.00617 ‡
Power law slope—frequency based	0.105	0.0499-0.14	0.129	0.0671-0.173	0.0933	0.0388-0.175	.111	NA	NA	NA
Power law y-intercept—frequency based (s^2/log Hz)	6.55	6.27-7.07	6.31	4.89-6.91	6.3	5.49-6.7	0.084	NA	NA	NA
Power law x-intercept—frequency based (log Hz)	−15.1	−60.4-17.3	−16.4	−47.4-27.1	−11.1	−33.7-44.7	.535	NA	NA	NA
Power law slope—histogram based	−0.288	−0.317 to −0.254	−0.306	−0.407 to −0.233	−0.265	−0.332 to −0.223	.166	NA	NA	NA
Power law y-intercept—histogram based (none)	−1.98	−2.16 to −1.85	−2.04	−2.52 to −1.85	−2.01	−2.25 to −1.88	.341	NA	NA	NA
Power law x-intercept—histogram based (log s)	−7.9	−8.49 to −6.07	−7.34	−9.2 to −6.09	−8.8	−9.66 to −6.7	.265	NA	NA	NA
DFA AUC (none)	−0.325	−0.452 to −0.169	−0.427	−0.789 to −0.18	−0.361	−0.61 to −0.224	.288	NA	NA	NA
DFA α overall (none)	0.668	0.567-0.784	0.59	0.464-0.687	0.596	0.431-0.669	.009	.00499 *	.746	.00653 ‡
DFA α 1 (none)	0.708	0.582-0.824	0.6	0.491-0.729	0.606	0.435-0.707	.012	.00897 *	.525	.0071 ‡
DFA α 2 (none)	0.487	0.284-0.578	0.37	0.183-0.485	0.338	0.146-0.496	.042	.0283 *	.572	.0224 ‡
Approximate entropy (none)	0.521	0.44-0.573	0.533	0.416-0.607	0.463	0.349-0.557	.133	NA	NA	NA
Wavelet AUC (none)	−3.4	−4.86 to −1.41	−4.36	−10.3 to −1.32	−3.64	−7.17 to −1.89	.342	NA	NA	NA
Poincare SD1 (none)	531	347-864	458	247-807	421	307-653	.297	NA	NA	NA
Poincare SD2 (none)	619	466-1000	553	270-894	537	328-684	.091	NA	NA	NA

Median and interquartile range are shown. For each measure, results of nonparametric ANOVA test are shown. Where the null hypothesis of equal median among the low, median, and high groups are rejected ($P < .05$), a post hoc Wilcoxon rank sum test was run to test for equality between groups pairs (low-medium, medium-high, and low-high). n indicates the number of days.

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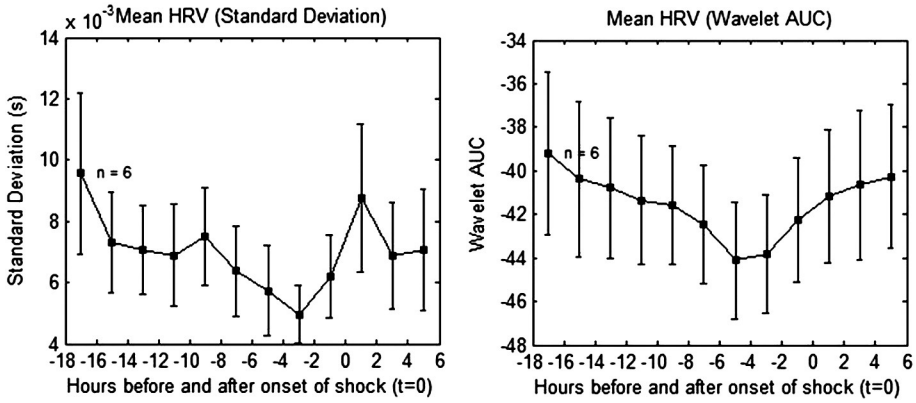

Fig. 3 Mean (±SEM) HRV trajectories encompassing 18 hours before and 6 hours after onset of shock (t = 0). Mean HRV (averaged 5-minute variability windows) for each 2-hour period plotted for all patients (n = 6).

rise in HRV after the onset of shock (averaged across all patients). Respiratory rate variability was also analyzed for 6 patients. As shown in Fig. 4, there was no obvious decline in RRV as early as 18 hours before shock; however, a slight downwards trend was observed between 12 and 6 hours before the onset of shock. A rise in variability post onset of shock was also observed for RRV.

3.3.2. Resolution of respiratory failure

Twelve patients who were extubated while on study had valid data for the HRV analysis. Of these, 9 extubations were successful, and 3 extubations failed. As shown in Fig. 5, patients who passed extubation had higher HRV on average leading up to and after extubation. Respiratory rate variability was analyzed for 14 extubations—12 successful and 2 failed. As shown in Fig. 6, patients who passed extubation experienced a steady increase in RRV starting between 10 and 8 hours before extubation compared with those who failed, where RRV was either steady or slightly declining in this same period. Respiratory rate variability measured by SD for patients with successful extubations was higher on average during the 18 hours leading up to extubation, but this observation is not as prominent with the other variability measures.

4. Discussion

The main objective of this exploratory study was to perform an observational analysis of both HRV and RRV monitoring in conjunction with daily measures of organ failure for critically ill patients. The results demonstrated an association between reduced HRV and RRV and organ dysfunction in critically ill patients, that is, HRV and RRV tend to be higher on days with low MODS scores compared with days with medium or high MODS scores. For patients undergoing monitoring around shock and extubation, several measures of HRV and RRV showed distinct trajectories beginning 12 to 18 hours beforehand.

Several studies have reported reduced variability in association with MODS, particularly with measures reflecting autonomic nervous activity [41]. Although we have

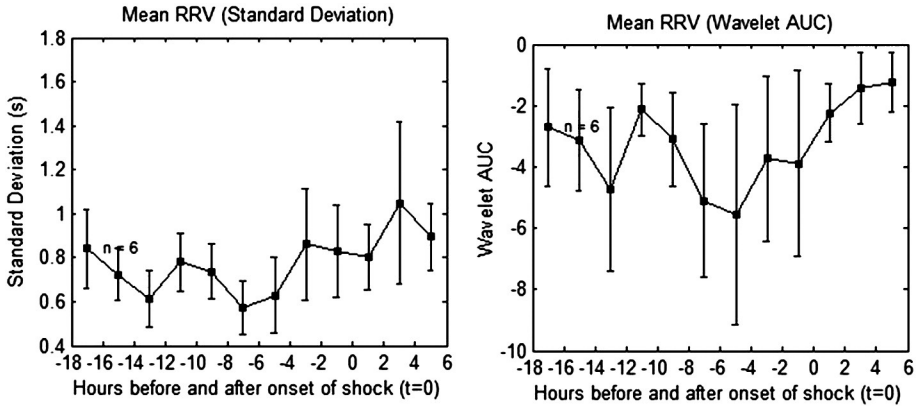

Fig. 4 Mean (±SEM) RRV trajectories encompassing 18 hours before and 6 hours after onset of shock (t = 0). Mean RRV (averaged 5-minute variability windows) for each 2-hour period plotted for all patients (n = 6).

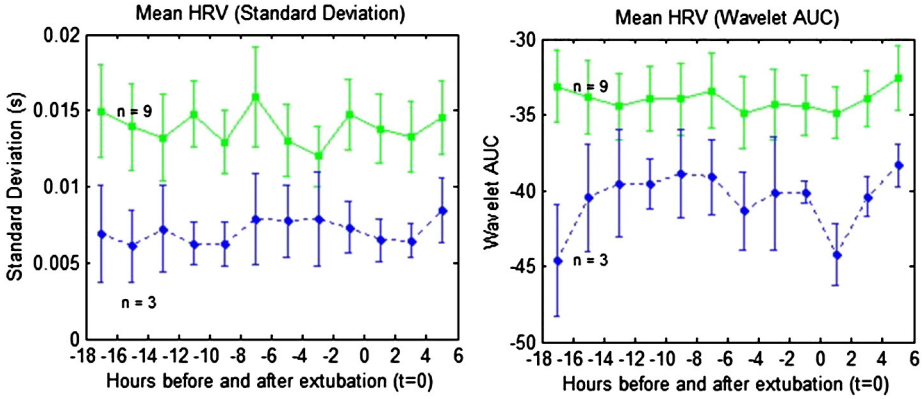

Fig. 5 Mean (±SEM) HRV trajectories encompassing 18 hours before and 6 hours after extubation ($t = 0$). Mean HRV (averaged 5-minute variability windows) for each 2-hour period plotted for all patients (n = 12 patients are included: 9 successful, 3 failed).

compared with MODS scores according to 3 categories of illness severity rather than 2 (eg, as in Papaioannou et al [36]), our results are consistent for SD and LF/low frequency to high frequency ratio (LF/HF)HF when comparing the low MODS and high MODS groups. They are not consistent, however, for approximate entropy (ApEn) which we found to be lower in less severely ill patients. It is possible that entropy measures, which have demonstrated effectiveness as a predictor of mortality [42], are sensitive to factors for which we did not control (eg, time of day of measurement, body position, medications, etc). We did observe higher ApEn on days with lower MODS when analyzing RRV, although the results were not statistically significant. There were no studies that we could find with which to compare RRV results in association with MODS.

For patients who experienced cardiac shock, the trajectory of several measures of HRV showed a downwards trend beginning as early as 18 hours before the onset of shock, with minimums occurring approximately 2 to 4 hours before the onset of shock. In general, HRV appears to outperform RRV as an indicator of onset of shock. The rise in HRV and RRV slightly before and following the onset of shock could be due to interventions initiated to treat the symptoms of the impending shock. We could identify no studies with which to compare these results (ie, a trajectory of variability leading up to the onset of shock), but our findings are consistent with those studies, which showed an association between septic shock and reduction of HRV [11,13]. Lastly, we have previously demonstrated loss of HRV in association with the onset of clinical diagnosis of infection in ambulatory non-critically ill patients, occurring on average 24 hours before clinical diagnosis [39].

In this study, we found that, for patients who experienced successful extubation, the trajectory of several measures of RRV showed an upwards trend beginning as early as 10 hours before the extubation. Sedation is known to affect biosignal variability in critically ill patients [43]—the extent to which decreasing sedation before the spontaneous breathing trial accounted for the increased respiratory variability in this group remains unclear. For the entire 18 hours analyzed, HRV values were on average higher for those patients who were successfully extubated compared with those who failed; however, no obvious upwards or downwards trend was observed for either group.

There are several limitations to this pilot study. The association between increasing organ failure and reduced HRV and RRV is based on a retrospective separation of patient-days into 3 groups of organ failure. It is important to note that the aggregated pool of patient-days (n = 189 for HRV and n = 174

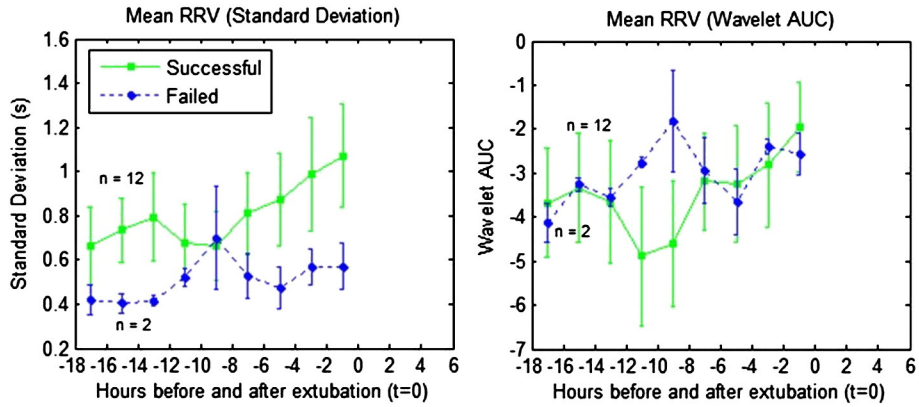

Fig. 6 Mean (±SEM) RRV trajectories encompassing 18 hours before and 6 hours after extubation ($t = 0$). Mean RRV (averaged 5-minute variability windows) for each 2-hour period plotted for all patients (n = 14 patients are included: 12 successful, 2 failed).

for RRV) included multiple days from the same patient. Thus, as a patient's MODS score changed throughout their ICU stay, patient-days for the same patient would have appeared in all MODS categories—high, medium, and low.

Lastly, an important caveat to bear in mind is that these preliminary results are reported on population-based averages and are not intended to imply that the patterns in vital sign variability seen in this study are "signatures" of various events in individual patients. The tracking of variability in individual patients proved challenging due to numerous confounding factors affecting variability, most notably sedation and interventions. Rather, these findings suggest a potential value in tracking cardiorespiratory variability over time, which merits further investigation. The small numbers of this investigation preclude a conclusive analysis, but rather serve to support hypotheses and prior literature linking reduced variability occurring in association with critical illness.

5. Conclusions

In this pilot study, for the first time, we have demonstrated that tracking both HRV and RRV over time with CIMVA offers a potential means to characterize severity of organ dysfunction on a daily basis. The loss of HRV before onset of shock and the rise in RRV before successful resolution of mechanical ventilation further support the potential utility of multiorgan variability monitoring to characterize a patient's physiologic responses to clinical events. No additional invasive monitor was required for this analysis, rather the results stem simply from a more efficient use of all data harvested at the bedside. This allows for the analysis of variability at any specific point in time or the analysis of data over time, so that deterioration can be tracked by visual inspection of the signals [11,13,37]. Taken together, these results support the assertions made by Voss [34], who noted that continuous individualized monitoring has the potential to be useful in identifying the progression or regression of a disease process and "could be a valuable addition to current physiologic based monitoring systems."

Acknowledgments

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